Reduced kidney transplant rejection rate and pharmacoeconomic advantage of mycophenolate mofetil

Wuthrich, R

Abstract: BACKGROUND: Several multinational controlled clinical trials have shown that triple therapy immunosuppressive regimens which include mycophenolate mofetil (MMF), cyclosporin A (CSA) and steroids (S) are superior compared with conventional regimens which include azathioprine (AZA), CSA and S, mainly because MMF reduces the rate of acute rejection episodes in the first 6 months after kidney transplantation. Post-marketing studies are useful to evaluate the general applicability and costs of MMF-based immunosuppressive regimens. METHODS: Based on the excellent results of the published controlled clinical trials, we have changed the standard triple therapy immunosuppressive protocol (AZA+CSA+S) to an MMF-based regimen (MMF+CSA+S) at our centre. To analyse the impact of this change in regimen, we have monitored 6-month patient and graft survival, rejection rate, serum creatinine and CSA levels, as well as the costs of the immunosuppressive and anti-rejection treatments, in 40 consecutive renal transplant recipients (MMF group) and have compared the data with 40 consecutive patients transplanted immediately prior to the change in regimen (AZA group). RESULTS: Recipient and donor characteristics were similar in the AZA and MMF groups. Patient survival (37/40; 92.5% in the AZA group vs 38/40; 95% in the MMF group), graft survival (36/40 vs 36/40; both 90%) and serum creatinine (137+/-56 vs 139+/-44 micromol/l) after 6 months were not significantly different. However, the rate of acute rejection episodes (defined as a rise in creatinine without other obvious cause and treated at least with pulse steroids) was significantly reduced with MMF from 60 to 20% (P=0.0005). The resulting cost for rejection treatment was lowered 8-fold (from sFr. 2113 to 259 averaged per patient) and the number of transplant biopsies was lowered > 3-fold in the MMF group. The cost for the immunosuppressive therapy was increased 1.5-fold with MMF (from sFr. 5906 to 9231 per patient for the first 6 months). CONCLUSIONS: The change from AZA to MMF resulted in a significant reduction in early rejection episodes, resulting in fewer diagnostic procedures and rehospitalizations. The optimal long-term regimen in terms of patient and pharmacoeconomic benefits remains to be defined

DOI: https://doi.org/10.1093/ndt/14.2.394

Nephrol Dial Transplant (1999) 14: 394–399

Nephrology
Dialysis
Transplantation

Original Article

Reduced kidney transplant rejection rate and pharmacoeconomic advantage of mycophenolate mofetil

Rudolf P. Wüthrich, Thomas Weinreich, Patrice M. Ambühl, Ann-Kathrin Schwarzkopf, Daniel Candinas and Ulrich Binswanger

Division of Nephrology, Departments of Internal Medicine and Surgery, University Hospital, Zürich, Switzerland

Abstract

Background. Several multinational controlled clinical trials have shown that triple therapy immunosuppressive regimens which include mycophenolate mofetil (MMF), cyclosporin A (CSA) and steroids (S) are superior compared with conventional regimens which include azathioprine (AZA), CSA and S, mainly because MMF reduces the rate of acute rejection episodes in the first 6 months after kidney transplantation. Post-marketing studies are useful to evaluate the general applicability and costs of MMF-based immunosuppressive regimens.

Methods. Based on the excellent results of the published controlled clinical trials, we have changed the standard triple therapy immunosuppressive protocol (AZA + CSA + S) to an MMF-based regimen (MMF + CSA + S) at our centre. To analyse the impact of this change in regimen, we have monitored 6-month patient and graft survival, rejection rate, serum creatinine and CSA levels, as well as the costs of the immunosuppressive and anti-rejection treatments, in 40 consecutive renal transplant recipients (MMF group) and have compared the data with 40 consecutive patients transplanted immediately prior to the change in regimen (AZA group).

Results. Recipient and donor characteristics were similar in the AZA and MMF groups. Patient survival (37/40; 92.5% in the AZA group *vs* 38/40; 95% in the MMF group), graft survival (36/40 *vs* 36/40; both 90%) and serum creatinine (137 ± 56 *vs* 139 ± 44 μmol/l) after 6 months were not significantly di erent. However, the rate of acute rejection episodes (defined as a rise in creatinine without other obvious cause and treated at least with pulse steroids) was significantly reduced with MMF from 60 to 20% ($P = 0.0005$). The resulting cost for rejection treatment was lowered 8-fold (from sFr. 2113 to 259 averaged per patient) and the number of transplant biopsies was lowered >3-fold in the MMF group. The cost for the immunosuppressive therapy was increased 1.5-fold with MMF (from sFr. 5906 to 9231 per patient for the first 6 months).

Conclusions. The change from AZA to MMF resulted in a significant reduction in early rejection episodes, resulting in fewer diagnostic procedures and rehospitalizations. The optimal long-term regimen in terms of patient and pharmacoeconomic benefits remains to be defined.

Key words: mycophenolate mofetil; pharmacoeconomy; rejection; renal transplantation

Introduction

Several large randomized controlled clinical trials have demonstrated that the novel immunosuppressive drug mycophenolate mofetil (MMF, CellCept®) significantly reduces the rate of early acute rejection episodes after renal allograft transplantation when compared with azathioprine (AZA) or placebo [1–4]. The pooled 1-year e cacy analysis of three clinical studies has shown that the MMF regimen reduced the rate of biopsy-proven acute rejection episodes from 40.8% in the AZA or placebo groups to 19.8% in the patients treated with 2 g of MMF per day [5]. Side e ects as well as infectious and neoplastic complications were similar with MMF.

Despite the excellent results on the rate of acute rejection episodes, the 1-year analysis has revealed that patient survival was not better with MMF (96%) compared with the placebo/AZA regimens (95.3%). The graft survival with MMF (90.4%) was also similar when compared with placebo or AZA (87.6%) [5]. Whether long-term benefits could result with the MMF regimen has not been investigated yet. The 3-year results suggest that a trend towards better graft survival can be obtained with MMF [6,7].

Aside from the documented advantage for the patient treated with MMF, another important issue is the cost of immunosuppression. Analyses at 1 year have shown that the use of MMF resulted in net savings despite increased total maintenance

Correspondence and o print requests to: Rudolf P. Wüthrich, Division of Nephrology, University Hospital, Rämistrasse 100, CH-8091 Zürich, Switzerland.

immunosuppression cost [8,9]. Whether MMF treatment is cost e ective beyond 1 year of treatment remains to be determined.

The general applicability of the excellent results obtained with MMF to individual transplant centres needs to be proven. By monitoring 6-month patient and graft survival, rejection rate, transplant function and cost, we assessed the short-term impact of a triple therapy regimen containing MMF instead of AZA at our centre.

Subjects and methods

Study design

We compared patient and graft survival, rejection rates, serum creatinine and cost of immunosuppression in 40 consecutive kidney transplant patients treated with MMF with a historical control group of 40 renal transplant patients treated with AZA. The standard immunosuppression (AZA group) was a triple therapy regimen which included the cyclosporin A (CSA) microemulsion Sandimmune Neoral® (initial dose 8 mg/kg, then tapering to achieve CSA levels between 150 and 250 ng/ml), prednisone (initial dose 1 mg/kg/day; then tapering to a dose of 10 mg/day within 6 months after transplantation) and AZA (1–1.5 mg/kg/day). Sandimmune was given intravenously at 3 mg/kg/day for the first 24 h. Sensitized patients, retransplants, patients with delayed graft function or patients receiving a transplant with donor age >65 received a 7-day course of Anti-Thymocyte Globulin (ATG) (Fresenius, 3 mg/kg/day i.v.) for induction treatment with delayed introduction of CSA. MMF was used at a dose of 2×1 g/day instead of AZA in the MMF group.

Outcome measurements

Donor and recipient characteristics were compared and examined for statistically significant di erences. Patient and graft survival rates were then determined after 6 months in both groups. Episodes of acute rejection—defined as a rise in serum creatinine not due to obstruction, hypovolaemia, cyclosporin toxicity or any other obvious cause and treated at least with pulse steroids (500–1000 mg for 3–5 days)—were recorded in both groups and the results of any biopsies were also checked. Serum creatinine, immunosuppression and cyclosporin levels were also recorded at 3 and 6 months and compared.

We also analysed the cost of the baseline immunosuppression and the costs of induction and rejection treatments in both groups. The cost of the baseline immunosuppression was estimated in Swiss Francs based on average doses used of Sandimmune Neoral® (300 mg/day), AZA (75 mg/day), MMF (2 g/day) and prednisone (20 mg/day) in the first 6 months after transplantation. Costs of the induction treatments with ATG (7×200 mg), and costs for rejection treatments were calculated based on average treatments with pulse steroids (5×1 g i.v. methylprednisolone), ATG Fresenius (7×200 mg) or OKT3 (7×5 mg). In addition, we recorded the number of transplant biopsies (reflecting the diagnostic activity due to presumed rejection) and examined the number of prolonged hospitalizations and rehospitalizations for treatment of rejection (reflecting supplemental hospital costs due to rejection).

Statistical analysis

All patient data were recorded on an Excel spreadsheet. Di erences in categorical variables between the two groups were analysed with Fisher's exact test with Yates' continuity correction, and donor and recipient age, cold ischaemia time and HLA mismatch were compared with Student's *t*-test. Patient and graft survival and rejection rates were also compared with Fisher's exact test. Serum creatinine, CSA levels and immunosuppressive doses at 3 and 6 months were compared with Student's *t*-test.

Results

Comparison of groups

A total of 80 patients were analysed in this study, including 40 historical control patients (AZA group) and 40 patients treated with a regimen containing MMF (MMF group). Table 1 demonstrates the baseline characteristics of the two groups. Both groups were similar with respect to age, sex, height, weight, cause of end-stage renal disease, presence or absence of panel-reactive anti-HLA antibodies (number of sensitized patients) and previous mode of dialysis. The number of patients who were retransplants was higher in the AZA group (5 *vs* 1; $P=0.2$).

The donor characteristics were also quite similar (Table 2). More recipients in the MMF group displayed delayed graft function (25% *vs* 12.5%; $P=0.25$) despite comparable cold ischaemia times of the grafts, reflecting perhaps the slightly higher age of the donors in the MMF group. The number of HLA-A, -B and -DR mismatches was also not di erent between donors and recipients, and the cytomegalovirus (CMV) constellations between donor and recipients were also similar.

E cacy

Table 3 shows that the 6-month patient survival rates were similar in both treatment groups (95% in the MMF group *vs* 92.5% in the AZA group). Likewise, the graft survival rates were not di erent (90% in both groups). The causes of death and graft failure are also reported in Table 3. Due to the low number of events, a significant di erence cannot be excluded.

The systematic use of MMF instead of AZA reduced the incidence of clinically diagnosed acute rejection episodes in the first 6 months after transplantation from 60% to 20% ($P=0.0005$). Table 4 demonstrates that steroid-sensitive episodes were the most frequent type of acute rejection, and their number was markedly reduced in the MMF group. The number of ATG or OKT3 treatments for steroid-resistant rejection was also reduced in the MMF group (due in part also to the recent availability in 1997 of FK506 to treat steroid-resistant rejection episodes). Table 4 also shows that the mean time to rejection was similar in both groups.

Table 5 demonstrates that significantly fewer diagnostic transplant biopsies were needed in the MMF group compared with the AZA group (8 *vs* 27).

Table 1. Baseline characteristics of renal allograft recipients

Characteristic	AZA group ($n=40$)	MMF group ($n=40$)
Inclusion period	8/1996–1/1997 (6 months)	2/1997–11/1997 (10 months)
Age (years)	46.6±11.8 (24–68)	47.2±13.0 (18–66)
Gender (M:F)	28:12	25:15
Height (cm)	171.5±9.7	169.2±9.1
Weight (kg)	70.2±12.4	69.8±11.1
Cause of renal failure		
Glomerulonephritis	12	18
Chronic TIN	7	6
Diabetes	2	2
Hereditary or PKD	9	5
Hypertension	2	1
Other	8	8
Type of transplant		
1. CAD	33	35
2. CAD	5	1
1. LRD	2	4
No. sensitized	3/40	4/40
Mode of dialysis		
HD	31	30
CAPD	8	9
None	1	1

Baseline recipient characteristics were recorded and analysed for di erences. Averaged data represent mean±SD. The recipient age range is indicated in parentheses. No statistically significant di erences were detected between the two groups.
CAD, cadaveric; CAPD, continuous ambulatory peritoneal dialysis; HD, haemodialysis; LRD, live related donor; PKD, polycystic kidney disease; TIN; tubulointestinal nephritis.

Table 2. Baseline donor characteristics

	AZA	MMF
Age (years)	37.6±14.5 (13–66)	44.1±15.4 (18–69)
Gender (M:F)	22:18	29:11
Cold ischaemia time (min)	772±359 (60–1815)	694±341 (90–1340)
Delayed graft function	5/40	10/40
HLA mismatch	3.6±1.0	3.7±1.2
CMV (D/R)		
−/−	7	8
−/+	5	8
+/+	20	16
+/−	8	8

Baseline donor characteristics were recorded and analysed for di erences. Averaged data represent mean±SD. The donor age and cold ischaemia time ranges are indicated in parentheses. No statistically significant di erences were detected between the two groups.

Table 3. Patient and graft survival rates after 6 months and causes of death and graft failure

	AZA	MMF
Patient survival	37/40 (92.5%)	38/40 (95%)
Graft survival	36/40 (90%)	36/40 (90%)
Causes of death	Carcinoma of pancreas Encephalitis Fulminant hepatitis	Sepsis, multiorgan failure Perforation of caecum, sepsis
Causes of graft failure:		
Death with functioning graft	3	2
Rejection	1	1
Technical	–	1

Patient and graft survival rates and the causes of death and graft failure are reported for both groups.

Table 4. Rejection episodes and therapy

	AZA	MMF
Rejection rate	60%	20%*
Patients with		
no rejection	16/40	32/40
1 rejection	13/40	5/40
2 rejections	7/40	2/40
3 or more rejections	4/40	1/40
No. of rejection treatments applied		
Steroid bolus	27	7
ATG or ATGAM	9	0
FK506	0	3
OKT3	2	1
Time to rejection (days)	12.3 ± 8.2	10.0 ± 4.1

The number of patients with none, 1, 2 and 3 or more rejection episodes in the first 6 months after transplantation is reported. Furthermore, the number of treatments with methylprednisolone bolus, ATG or ATGAM, FK506 ('rescue') or OKT3 is indicated, demonstrating that MMF markedly reduces the incidence of acute rejections and the number of treatments. No change in time to rejection is seen.
*$P < 0.0005$.

Table 5. Diagnostic biopsies and rejection type (Ban)

	AZA	MMF
Normal	7	3
Non-specific or borderline	10	3
Ban grade I	9	1
Ban grade IIa	0	0
Ban grade IIb	1	1
Total no. of biopsies	27	8

The number of diagnostic biopsies in the first 6 months after transplantation and the Ban grading is reported. Significantly fewer biopsies were performed in the MMF group.

Classification of these biopsies according to the Ban scheme [10] revealed that the histopathological lesions were similar in both groups, with more than half of the biopsies showing a normal histology or non-specific changes.

The serum creatinine values at 6 months were also not di erent in the two groups (137 ± 56 μmol/l in the AZA group *vs* 139 ± 44 in the MMF group). Table 6 shows that the average daily doses of prednisone and cyclosporin did not di er at any time between the two groups, nor was there a significant di erence in the cyclosporin levels. More patients were treated with ATG induction in the MMF group (57.5% *vs* 40%; $P = 0.18$). This could have influenced the rejection rate slightly.

Side e ects

Treatment failures were low and comparable in both groups. The number of patients with functioning graft at 6 months on the initial triple regimen (MMF + prednisone + CSA) was 32/36, compared with 35/36 with the AZA + prednisone + CSA regimen.

During the 6-month observation period, no serious adverse events were recorded in either group that could be ascribed to either the immunosuppressive regimen or to a single immunosuppressive drug. The occurrence and the course of CMV infections was similar in both groups: five patients developed non-invasive CMV disease in each group. There were no *Pneumocystis carinii* infections in both groups. The MMF regimen was well tolerated, and gastrointestinal side e ects were rare. The MMF dosage had to be reduced temporarily in six patients due to CMV infection ($n = 4$), leukopenia ($n = 1$) or anaemia ($n = 1$).

Costs

Table 7 indicates the cost of the two regimens averaged per patient for the 6-month period. Whereas the immunosuppression therapy was 1.8-fold more expensive with MMF, 8-fold greater costs arose from the treatment of the more frequent rejection episodes in the AZA group. Due to the higher number of induction treatments in the MMF group (23 *vs* 16), more expenses resulted from ATG induction treatments in the MMF group. The total estimated costs for immunosuppressive drugs was 24% higher in the patients in the MMF group in the first 6 months.

Important additional savings could be documented in the MMF group, although the amount of these costs could not be estimated. For example, 3-fold less diagnostic biopsies were required in the MMF group (Table 5). Transplant biopsies can be regarded as an indicator of diagnostic activities around a rejection episode, and certainly there were also fewer laboratory tests and radiological procedures such as transplant ultrasound examinations in the MMF group. In addition, in the MMF group, there were also fewer prolonged hospitalizations and rehospitalizations for the treatment of steroid-resistant rejection episodes, which generally require central line placement and i.v. ATG treatment (data not shown).

Discussion

This study reports on the successful use of MMF instead of AZA after renal allograft transplantation at a single centre. The change from AZA to MMF decreased the 6-month rejection rate 3-fold from 60 to 20%. Our data are in agreement with the previously reported international trials [1–4] and demonstrate that an individual centre can successfully reduce the rate of acute rejection episodes in renal transplant patients when changing from an AZA-containing to an MMF-containing triple therapy regimen. The additional benefits of this treatment strategy are a lower requirement for diagnostic procedures and fewer rehospitalizations for treatment of steroid-resistant rejection episodes.

Our study is the first to document enhanced e ectiveness of MMF compared with AZA in Sandimmune Neoral® (CSA microemulsion)-treated patients; the previously published studies were all performed with

Table 6. Comparison of the immunosuppressive regimens

	AZA		MMF	
Initial regimen				
Sandimmune i.v.	3 mg/kg/day		3 mg/kg/day	
Neoral p.o.	8 mg/kg/day		8 mg/kg/day	
Prednisone	1 mg/kg/day		1 mg/kg/day	
MMF	–		2000 mg/day	
AZA dose	1–1.5 mg/kg/day		–	
ATG induction	16/40 (40%)		23/40 (57.5%)	
Maintenance regimen	At 3 months	At 6 months	At 3 months	At 6 months
Neoral p.o. (mg/day)	271 ± 82	253 ± 74	261 ± 75	247 ± 69
Prednisone (mg/day)	19 ± 5	10 ± 3	16 ± 5	10 ± 0
MMF (mg/day)	–	–	1742 ± 435	1950 ± 201
AZA (mg/day)	74 ± 17	72 ± 19	–	–
CSA level (ng/ml)	202 ± 51	198 ± 47	216 ± 64	207 ± 66

The initial regimen, the use of ATG induction therapy with ATG Fresenius and the mean ± SD dosages of cyclosporin, prednisone, azathioprine and mycophenolate mofetil are reported at 3 and 6 months for both groups.

Table 7. Estimated cost of immunosuppression

	AZA	MMF
Immunosuppression	5906	9231
Induction with ATG	2536	3646
Rejection treatment	2113	259
Total cost	10 555	13 136

Cost of immunosuppression, induction and rejection treatments were averaged per patient for the 6-month period and are indicated in Swiss Francs. Calculations were based on an average daily use of 2 × 150 mg of CSA, 75 mg of AZA or 2 × 1000 mg of MMF, and 20 mg of prednisone. Average induction therapy was with ATG (200 mg/day for 7 days), and rejection treatments were with methylprednisolone pulses (1000 mg/day for 5 days), ATG (200 mg/day for 7 days) or OKT3 (5 mg/day for 7 days).

the older preparation of Sandimmune. Our study also demonstrates that a single centre can easily document the impact of a novel immunosuppressive drug such as MMF by recording patient data regularly and by performing a comparison with a historical group.

Despite being more expensive than AZA, immunosuppressive treatment with MMF was cost e ective during the first 6 months. Our study shows that reduced costs could be obtained due to the lower number of rejection episodes necessitating expensive diagnostic activity such as transplant biopsies, rejection treatments and rehospitalizations. Sullivan *et al.* [8] have analysed the cost-e ectiveness of MMF in the US multicentre trial and concluded that patients on MMF had slightly lower first year costs than the AZA-treated patients. So far, however, MMF has not been shown to improve graft survival after 1 and 3 years. Being an expensive drug, it remains to be determined whether cost-e ectiveness is maintained when treating beyond 1 year. However, an unmeasured advantage of the reduced number of rejections with MMF treatment is certainly the comfort and the psychological benefit of not needing rejection treatments.

In summary, we have shown that when switching the AZA-based triple therapy immunosuppressive protocol to an MMF-based protocol, the 6-month rejection rate at our centre was reduced from 60 to 20%. With the approach of monitoring patient data over 6 months and comparing with a historical control, we were able to detect the beneficial e ect of MMF on the rejection rate very rapidly. The pharmacoeconomic advantage of using MMF for 6 months is reflected in the reduced number of diagnostic procedures and treatment costs for rejection episodes. Whether treatment with MMF beyond 6 months is necessary and cost e ective remains to be determined.

Acknowledgements. Part of these data was presented at the 3rd International Conference on New Trends in Clinical and Experimental Immunosuppression in Geneva in February 1998.

References

1. Sollinger HW, for the US Renal Transplant Mycophenolate Mofetil Study Group. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. *Transplantation* 1995; 60: 225–232
2. European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet* 1995; 345: 1321–1325
3. Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. *Transplantation* 1996; 61: 1029–1037
4. Wiesel M, Carl S, for the European Mycophenolate Mofetil Cooperative Study Group. A placebo controlled study of mycophenolate mofetil used in combination with cyclosporine and corticosteroids for the prevention of acute rejection in renal allograft recipients: 1-year results. *J Urol* 1998; 159: 28–33
5. Halloran P, Mathew T, Tomlanovich S, Groth C, Hooftman L, Barker C. Mycophenolate mofetil in renal allograft recipients: a pooled e cacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. The International Mycophenolate Mofetil Renal Transplant Study Groups. *Transplantation* 1997; 63: 39–47
6. Tomlanovich S, Cho S, Hodge E *et al.*, for the US Mycophenolate Mofetil Study Group. Mycophenolate mofetil in cadaveric renal transplantation: 3-year data. *Proceedings of the American Society of Transplant Physicians ASTP*, 1997
7. Mathew TH, for the Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. A blinded, long-term,

randomized multicenter study of mycophenolate mofetil in cadaveric renal transplantation: results at 3 years. *Transplantation* 1998; 65: 1450–1454
8. Sullivan SD, Garrison LP, Best JH. The cost e ectiveness of mycophenolate mofetil in the first year after primary cadaveric transplant. *J Am Soc Nephrol* 1997; 8: 1592–1598
9. Louis-Touizer C, Nuijten MJ, Bayle F *et al.* Apport économique du mycophénolate mofétil comme traitement immunosuppresseur prophylactique après transplantation rénale de cadavre. *Presse Med* 1996; 25: 1577–1582
10. Solez K, Axelsen RA, Benediktsson H *et al.* International standardization of criteria for the histologic diagnosis of renal allograft rejection: the Ban working classification of kidney transplant pathology. *Kidney Int* 1993; 44: 411–422

Received for publication: 28.7.98
Accepted in revised form: 6.10.98